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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,724	09/22/2000	Pramod K. Srivastava	8449-128-999	1804
20583	7590	07/07/2004	EXAMINER YAEN, CHRISTOPHER H	
JONES DAY 222 EAST 41ST ST NEW YORK, NY 10017			ART UNIT 1642	PAPER NUMBER

DATE MAILED: 07/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,724	SRIVASTAVA, PRAMOD K.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31,71 and 76-93 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31,71 and 76-93 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Re: Srivastava *et al*
Priority Date: 02 June 2000

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/24/2004 has been entered.
2. Claims 1-30, 32-70, 72-75 are canceled without prejudice or disclaimer. Claims 92-93 are newly added.
3. Claims 31, 71, and 76-93 are pending and examined on the merits.

New Arguments

Claim Rejections - 35 USC § 112, 1st paragraph

4. Claims 31, 71, 76, and 80-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has only set forth a purified antibody as the "compound" which interferes with the interaction of a first heat shock protein (HSP) with the α 2 macroglobulin receptor

(α 2MR), and therefore the written description is not commensurate in scope to claims that read on generically any and all compounds, such as “antagonist”, “small molecule” or “peptide” molecules as broadly claimed. The following *written description* rejection is set forth herein.

The claims recite a “purified compound”, “antagonist”, “small molecule”, and “peptide” as part of the invention. However, there does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides the recited function of interfering with the interaction of a first heat shock protein with an α 2MR. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 “Written Description” Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant does not appear to have reduced to practice the broadly claimed genus of compounds, antagonists, small molecules, or peptides. Neither has Applicant provided a sufficient written description of any structure that may be correlated with the desired function. A “compound”, “antagonist”, “small molecule”, and “peptide”

Art Unit: 1642

encompass *any* molecule with the functional activity of interfering with the interaction of a first HSP with the α 2MR. Thus the genus of compounds encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

While it is noted that the instant claims are drawn to methods, the claims nevertheless require an adequate written description of the "compound", "antagonist", "small molecule" and "peptide" employed in the methods.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Claim Rejections - 35 USC § 112, 1st paragraph

5. Claims 31,71,76, and 77-93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims of the instant invention are drawn to a method of modulating or inhibiting an immune response comprising the administration to a human a purified compound that either interferes with the interaction of a first heat shock protein with the $\alpha 2$ MR or binds to with the $\alpha 2$ MR thereby inhibiting the immune response. The specification teaches that the $\alpha 2$ MR is a receptor for HSPs (such as gp96, HSP70, and HSP90). The specification also provides prophetic embodiments of the invention such the screening of antagonists/agonists, the use of the antagonists/agonists for the treatment of various diseases, such as cancer, infectious diseases, and autoimmune diseases. However, one of skill in the art cannot reasonable predict the outcome of the in vivo administration of purified compounds as broadly claimed for the treatment of diseases such as cancer, infectious diseases, and autoimmune diseases, based on the specification as originally filed. Reasonable correlation between what is claimed and what is taught in the specification or in the art at the time the invention was made must be present for one of skill in the art to practice the invention commensurate in scope to the claims.

There is insufficient guidance and objective evidence in the specification that the administration of compounds in general, especially, antibodies would be indicative of modulating an immune response or inhibiting an immune response; wherein it would not be predictable to one of skill in the art to use the method in order to modulate or inhibit an immune response in any individual. Currently, the specification has only provided in vitro examination of a receptor-ligand interaction, and has not provided sufficient correlation between such examination to the actual reduction or modulation of an immune response in a individual. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of

Art Unit: 1642

histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, as it specifically applies to the treatment of cancer, it is generally known and accepted in the art that the treatment of cancer is at most unpredictable. Gura (Science, v278, 1997, pp.1041-1042) discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic

Art Unit: 1642

assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Further, Bellone *et al.* (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where “there is usually a poor correlation between induction of specific T-cells and the clinical responses” (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). Indeed, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489) chose to evaluate the Wilm’s tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic cells. However, WT1 peptide immunization did not show any effect on tumor growth in-vivo (Figure 10, page 1486). All of this underscores the criticality of providing workable examples, which are not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to use the pharmaceutical compositions or vaccine formulations as contemplated in the disclosure.

Art Unit: 1642

Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 31,71,76, and 80-91 are rejected under 35 U.S.C. 102(e) as being anticipated by Nuijens *et al* (US 6,333,311, claims priority to 60/036,859 filed 3 February 1997). Nuijens *et al* teach the administration of a purified human lactoferrin for the modulation of an immune response (see col. 12, lines 10-23), wherein the modulation is antagonistic (i.e. inhibiting, see col. 2, lines 4-5). The specification of the instant invention defines a “compound” as any molecule which has the potential to interfere with the interaction of HSP with α 2MR (see page 7-8 for example), and because lactoferrin is a ligand for α 2MR (see page 3, line 29-30) it would inherently interfere with the binding of HSP to α 2MR. Furthermore, Nuijens *et al* teach that the administration of the lactoferrin is in response to an autoimmune disease (see col. 13, line 15), an infectious disease (see col. 12, lines 42-45), and cancer (see col. 2, line 28), wherein the autoimmune diseases is rheumatoid arthritis (col. 13, line 15), the infectious

Art Unit: 1642

disease is caused by herpes simplex virus I (col. 13, line 42), and the cancer is either a solid tumor (of which can be benign or malignant) or a leukemia (Jurkat cells are a primary leukemia cell line, see col. 23). Although not specifically disclosed, the method of Nuijens *et al* would inherently blocked the binding of HSPs in general to the α 2MR, and therefore claims that read on specific HSP (i.e. claims 80-82) are anticipated, in the absence of factual evidence to the contrary. Moreover, because the specification has not specifically defined the metes and bounds of the term “small molecule” or “peptide” the lactoferrin protein is interpreted as being either a small molecule or a peptide, and therefor is also anticipated.

Claim Rejections - 35 USC § 102

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 31,71,76,78,80-85, and 91-93 are rejected under 35 U.S.C. 102(b) as being anticipated by Hyman BT *et al* (WO 97/04794). Hyman BT *et al* disclose a method of using agents to reduce (i.e. antagonize) the binding of a ligand to the LRP (also known as α 2MR), wherein the agents are antibodies or peptides (see for example page 8). This binding would inherently modulate an immune response because the agents used would block the binding of HSPs (i.e. gp96, HSP70, HSP90) to the LRP). Because the specification has not defined “dense deposit disease” and because Alzheimer’s disease is characterized as a disease involving the deposit of extracellular plaques (as evidenced by Weiner *et al* (Nature Dec 2002;420:879-884)), the claims are

Art Unit: 1642

also anticipated. Moreover, because the specification has not specifically defined the metes and bounds of the term "small molecule" or "peptide" the lactoferrin protein is interpreted as being either a small molecule or a peptide, and therefor is also anticipated. And finally, Hyman BT *et al* teach that the antibodies to LRP can be monoclonal (page 13), polyclonal (page 13), humanized/chimeric (page 16), single chained, F(ab), or Fab(2) fragments (page 13). Single chain antibodies, Fab, and Fab(2) comprise an epitope binding domain, and therefore the claim drawn to compounds that comprise epitope binding domains are also anticipated (claim 93).

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 2/24/2004.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1642

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
May 25, 2004



GARY NICKOL
PRIMARY EXAMINER